Teaching Biotechnology to Medical Students: Is There An Easy Way?[1]

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ABSTRACT. **The practice of medicine by future physicians is going to be greatly influenced by knowledge obtained from biotechnology. For instance, the development of DNA-based, prenatal diagnoses for inherited genetic disease or the availability of cloned protein hormones or vaccines will require that physicians have a different basic science background than their predecessors. This will necessitate changes in how the basic sciences are taught in medical schools. Suggestions are offered regarding the teaching of biotechnology to medical students.**

OHIO J. SCI. 87 (5): 158-161, 1987

INTRODUCTION

Over the last few years it has become very clear to those who read the scientific literature that there has been an almost exponential growth in the number of articles that involve genetic engineering, recombinant DNA, or some other aspect of biotechnology (Schmidtke et al. 1986). Indeed, Schmidtke et al. (1986) speculated that if the present growth in the number of reports of cloned genes was maintained, their number would be greater than all other scientific publications by 1994. Many of these articles relate to questions that affect directly or indirectly the lives of many people. Examples include the genetics of color vision (Nathans et al. 1986), the understanding of the LDL receptor system (Sudhof et al. 1985), the analysis of genetic diseases (Williamson 1985, Wion et al. 1986), development of sensitive assays for malaria (Guntaka et al. 1986), and the development of new strains of agricultural products (Marx 1985). In a recent meeting at Cold Spring Harbor on the "Molecular Biology of *Homo sapiens*" (Lewin 1986a), McKusick (1986a) noted that the number of isolated human genes had doubled in the last four years, and that the number of autosomal assignments increased five-fold in the last 10 years (McKusick 1986b). At the same meeting, Gilbert (Lewin 1986b) speculated on the feasibility of sequencing the whole human genome, which has some 3×10^9 nucleotides. To some, these articles and statements are indicative of the exciting and novel time that we live in, but to the majority, these events either may not be understood or misunderstood. Clearly, an effort has to be made to educate and/or inform people about the benefits of biotechnology, while at the same time pointing out any potential problems that may arise from its widespread applications. The question then becomes how, when, and where does this education start?

Many aspects of biotechnology must be taught to medical students. However, the basics of biotechnology should also be explained to college undergraduates, and even high school seniors, with the proviso that the basics are explained in a way that is interesting and easy to understand. One of the quickest ways to lose a student audience is to give boring lectures. For example, there is nothing to be gained from showing students one DNA sequence after another, since most of the information contained in these sequences is of interest to only a few scientists. Somehow the key point of the DNA sequence, say, of an insect globin gene, has to be simply summarized and clearly stated. For example, there are no introns in insect globin genes (Antoine and Niessing 1984); this makes the system different from that of humans and other eucaryotes. Once this point has been mentioned, the actual sequence of nucleotides, and so on, becomes irrelevant. A wide variety of globin gene families can easily be compared with each other or to plant leghemoglobins (which have three introns), without ever having to show a single DNA sequence. Naturally, there has to be a reason for the comparison; otherwise the students first get confused, then stop paying attention to the lectures. It is obvious that an explanation of why the globin gene families are being compared has to be first given to the students.

The following discussion will focus on the teaching of biotechnology to medical students. Suggestions will also be offered on teaching undergraduates and high school seniors.

BIOTECHNOLOGY AND THE MEDICAL STUDENT

At Northeastern Ohio Universities College of Medicine (NEOUCOM), there is no formal course in molecular biology, but the last half of the fall semester of biochemistry (which is taught all three semesters) covers topics such as nucleotide biosynthesis, DNA and RNA structure, gene organization, and prenatal diagnosis. The students are told very early in the course that, when they graduate, patients may ask them about DNA-based, prenatal diagnoses, or they may be prescribing insulin and growth hormone to patients, both of which can be obtained from genetically engineered bacteria. This is one of the background "reasons" for the students having to learn this material. The value of the recombinant DNA products is also explained briefly in terms of supply, cost, and purity. The latter is of particular importance because of the recent deaths of several patients who had received cadaveric human growth hormone (Koch et al. 1985).

The lectures in the fall semester focus on the red cell; the last seven weeks use replication, transcription, and translation as a means of explaining globin synthesis. The series gets tied together by a detailed analysis of the molecular basis of the thalassemias. This detailed analysis enables examples of gene mutations, population genetics, and pre-natal diagnosis to be brought to the attention of the students. A textbook is not used for this section of the

[1]Manuscript received 8 September 1986 and in revised form 23 February 1987 (#86-37).

semester, primarily because the information on thalassemias, prenatal diagnosis, cloning, and the like, is changing so rapidly. The students are given basic older information plus selected examples from the recent literature. This requires the lecturers to spend an enormous amount of time reading the literature and culling and processing suitable material. However, a benefit resulting from this effort is that the medical students find this "new" information quite interesting and begin to appreciate how rapidly knowledge is accumulating. An excellent example of this is the knowledge regarding the thalassemias. For a long time, most of the available information was about β thalassemia; however, over the last one to two years, an enormous amount of data has become available regarding the α thalassemias. In fact, α thalassemia is now regarded as the most common single gene disease in the world (Flint et al. 1986). A constant searching of the literature for teaching material really pays off. For example, the inheritance of homozygous α°thalassemia is lethal, and is referred to as *hydrops fetalis* (Kan 1986). There is one example (published in an abstract form), however, of a Chinese infant who was born prematurely and transfused before the diagnosis was established. The infant has reached the age of one year with monthly transfusions; his future physical and mental development might indicate whether heroic treatment for α°thalassemia is warranted (Yanofsky et al. 1984). This exception raises many economic, social, and ethical issues, which will be addressed for the first time by NEOUCOM medical students during the fall, 1986, lectures.

Occasionally, ethical issues are mentioned in the classroom, but in a careful, neutral manner. Material is used from such diverse sources as the *Medical Journal of Australia* (Bell and Pearn 1985, Garber et al. 1985) or the *Wall Street Journal* (Otten 1985). However, care is taken to inform the students, not persuade them, and to introduce ethical questions only when they are relevant to a particular concept or lecture. It is useful to give the students, as part of the day's handout, the complete text of the articles both for and against an issue. The main points are then mentioned only during the lecture, letting the students read the complete articles at their leisure. Because much of this information is subject to debate, we stress that this information will not be part of the final examinations.

In the second and third semesters of biochemistry, a limited number of lectures are given in more specialized areas. Several lectures are presented on protein and peptide hormones. These cover the cloning of insulin and growth hormone, and analyses of the growth hormone, pro-opiomelanocortin, and enkephalin gene families. Examples of restriction enzyme and southern blotting analysis of DNA isolated from families with growth hormone gene deletions are also presented. At this stage two points are made to the students. First, that some patients (i.e., those homozygous for the growth hormone gene deletion) do not respond to growth hormone treatment because they recognize growth hormone as a foreign protein and raise antibodies to it. Second, the ethical problem of growth hormone use and abuse (Milner 1986, Taylor 1986), which is: should growth hormone be a controlled substance?

Two lectures are also given on the analysis of diseases of unknown origin. These focus on the current knowledge regarding the diagnosis of diseases such as Duchenne muscular dystrophy, Huntington's disease, and so on, using restriction fragment length polymorphism (RFLP) analysis of human DNA samples (Monaco et al. 1985, Folstein et al. 1985). These lectures present what are probably two of the most difficult concepts in gene analysis: the relationship of RFLPs to gene inheritance, and the usefulness of localizing a defective gene to a region covering some $1\text{-}5 \times 10^6$ nucleotide pairs on a particular chromosome. Selected material from the literature can illustrate the difficult concepts to students. For instance, the excellent example of RFLPs around a normal insulin gene (White 1985), or the use of chromosomal karyotyping of Wolf-Hirschorn patients, with subsequent DNA analysis, to localize the Huntington's disease gene to the tip of the short arm of chromosome 4 (Gusella et al. 1985), are helpful. Neither of these examples are in textbooks; they were obtained from diligent reading of the scientific literature, then melded into the lectures. This constant updating of lecture material helps to hold the interest of the students.

Overall, the students get a comprehensive exposure to the role that biotechnology will play in their careers. The biochemistry department is currently discussing an increase in the time allotted for topics related to biotechnology. It seems that every week another new and/or important protein is cloned. Recent examples are the estrogen and glucocorticoid receptors (Green et al. 1986, Govindan et al. 1985). It is questionable how much of this new material the medical student should know. If necessary, some part of the traditional biochemistry course must be replaced, because the biochemistry course has only a finite number of allotted teaching hours.

At the moment, the biochemistry faculty at NEOUCOM feel that a reasonable balance has been achieved between covering the traditional topics of biochemistry and presenting the latest advances in the understanding of the molecular basis of diseases. However, this requires an increasing amount of effort to keep the lectures current and comprehensive.

BIOTECHNOLOGY AND THE UNDERGRADUATE

There are distinct advantages to providing either a separate biotechnology-oriented course to undergraduates or to ensuring that the topic is covered in existing biology or biochemistry courses. As biotechnology is now part of the real world, a suitable background would enable students to be more appreciative of the important health, social, and environmental issues relating to biotechnology. They would also be better prepared to make career decisions regarding graduate school programs. It is projected that there will be a shortage of trained biotechnologists in the near future (Rigl 1986). In response to this, at least one college (State University of New York at Fredonia), has instituted a special biotechnology degree program. The development of new courses, programs, or the inclusion of biotechnology into existing programs or courses, is not without cost. New faculty may have to be hired, or present faculty members convinced that they should be teaching something about which they have no knowledge or even interest.

Irrespective of the mechanism chosen for increasing the time given to the teaching of biotechnology, there are at least two major decisions to be considered. One is departmental support for this teaching; the other is a commitment by the lecturer to constantly update the information that is presented. The tendency is to use one textbook, that is often out of date even when first published, until a newer edition is published or a slightly more up-to-date alternative is available. Biotechnology is changing too fast and is too important to be treated so lightly. However, it must be recognized that a department's resources are limited and not always available for new and innovative approaches to teaching.

With some planning it should be possible to introduce some aspects of biotechnology into many undergraduate courses. Interesting data are now available regarding the origin of the serine proteases (Rogers 1985) which would fit nicely into a biochemistry course. The data on DNA fingerprinting could be included in a genetics course (Newmark 1986); the Food and Drug Administration's approval of a genetically engineered vaccine for hepatitis B could be discussed in an immunology course (Castro 1986). Whatever data are used, a conscious effort has to be made by someone to seek out the information and to work it into the lecture material, since every month there are more examples of new uses for products derived from biotechnology.

CHALLENGE OF TEACHING BIOTECHNOLOGY TO HIGH SCHOOL SENIORS

If certain aspects of biotechnology are going to be taught to high school students, then they have to be taught in a simple, clear, interesting, and understandable manner. Most of the students will not have the background for detailed explanations of cloning or bacterial genetics, nor is it necessary that they should. It should be possible to explain much of the "recombinant DNA aspects of biotechnology" through an understanding of only a few basic concepts such as the hydrogen bonding of nucleic acids, or specificity of restriction enzymes. The use of simple analogies are invaluable. For instance, the action of a zipper can be used to explain two complementary strands of nucleic acids. A system using different colored velcro strips could also be devised to represent double-stranded DNA and single-stranded RNA, to explain complementarity, or to show the principles of hybridization. Similarly, strips of different lengths could be used to demonstrate the stability of hydrogen bonding (i.e., the more hydrogen bonds or nucleotides, the more stable the double-stranded molecules).

If one wanted to explain the possible deleterious results of genetic mutations to seniors, one could go into a detailed explanation of the changes occurring in going from one nucleotide to another, alterations in hydrogen binding, amino acids, and so on. The result of this approach is a bored student. An alternative is to simplify the system by imagining that the information contained in a DNA sequence is given by the sentence: THE CAT SAT ON A MAT. The 3-letter groups are nucleotides; the word is an amino acid; the sentence represents useful information. Now it is easy to comprehend the results of a frameshift or deletion mutation. A possibly harmless mutation, where one amino acid is substituted for a similar amino acid, would be explained as THE rAT SAT ONA MAT. Clearly, the information from the "sentence" is essentially the same. Even or uneven crossovers are easily explained using this simple sentence system. This method is used to teach genetic mutations to medical students. Once the basics are understood, then specific examples are given with the clinical results. First, however, the students must learn a simple, basic set of examples.

It is also important that the science teachers responsible for disseminating this or other information be educated in the basics of biotechnology. This represents a distinct problem. Many science teachers will have had, at best, a limited exposure to the subject matter in college, with probably no further education in this area. It would be difficult for them to teach something that they do not really understand. Conceivably, summer workshops could be used to train selected high school science teachers. Care should be taken, however, in choosing the visiting lecturers. The fact that a lecturer has an extensive knowledge of biotechnology does not necessarily mean that that individual has the ability to express it in a clear, simple manner.

CONCLUSION

At NEOUCOM, the constant updating of the biochemistry lectures, coupled with the presentation of new material on prenatal diagnosis, gene organization, or some other aspect relating to human disease has helped keep Biochemistry-Molecular Pathology a popular and successful course. The extra time spent by the faculty in doing this is rewarded by very high attendance at both lectures and laboratories.

Most student evaluations also support our view that the course is successful. When asked "what did you find *most valuable* about this course", the latest (fall, 1986) comments included: "going to lectures"; "lectures concerning southern blot techniques and prenatal diagnosis"; "genetic section of course made sense for the first time"; and "I felt I learned a great deal of material that I can take with me and apply in a medical practice especially concerning hemolytic anemia and genetics (recombined DNA, and so on)". However, not all students are convinced. Under *least valuable,* there were: "the last couple of sessions in cloning. Just a little above my head"; and "the stress on the genetic basis of disease was inappropriate. Why do we need to know all the techniques of cloning DNA and genes just because one of the faculty does research in that area? A majority of the class was devoted just to gene technology. I think that this is far too much."

The experience at NEOUCOM also indicates that material related to biotechnology could be introduced into undergraduate and high school curricula. How feasible this would be is hard to tell. University and high school instructors have a greater teaching load than medical school faculty, and may not have the time or the opportunity to screen the literature for the latest relevant information. This is unfortunate because new information helps attract the students' interest, and biotechnology is here as part of our daily life, whether we like it or not. Publications such as *Science* or *Scientific American* do provide current information, but there is nothing like, for

example, seeing an article on Bloom's syndrome (Willis and Lindahl 1987) just before updating the next semester's lectures.

LITERATURE CITED

Antoine, M. and J. Niessing 1984 Intron-less genes in the insect *Chirononus thummi thummi*. Nature 310: 795-798.

Bell, J. A. and J. H. Pearn 1985 Prenatal cytogenetic diagnosis: medical and social implications. Indications, acceptance by doctors and patients, impact and cost: a 10-year review. The Medical J. of Australia 143: 76-79.

Castro, J. 1986 A breakthrough for biotechnology. The first genetically engineered vaccine for humans is approved. Time Aug. 4, 52.

Flint, J., A. V. A. Hill, D. K. Bowden, S. J. Oppenheimer, P. R. Sill, S. W. Serjeantson, J. Bana-Koiri, K. Bhatia, M. P. Alpers, A. J. Boyce, D. J. Weatherall, and J. B. Clegg 1986 High frequencies of α-thalassemia are the result of natural selection by malaria. Nature 321: 744-750.

Folstein, S. E., J. A. Phillips, D. A. Meyers, G. A. Chase, M. H. Abbott, M. L. Franz, P. A. Waber, H. H. Kazazian, P. M. Conneally, W. Hobbs, R. Tanzi, A. Faryniarz, K. Gibbons, and J. Gusella 1985 Huntington's disease: Two families with differing clinical features show linkage to the G8 probe. Science 229: 776-779.

Gerber, P., J. H. Pearn, and J. A. Bell 1985 Prenatal cytogenetic analysis: Some potential legal implications. The Medical J. of Australia 143: 80-83.

Govindan, M. V., M. Devic, S. Green, H. Gronemeyer and P. Chambon 1985 Cloning of the human glucocorticoid receptor cDNA. Nucl. Acids Res. 13: 8293-8304.

Green, S., P. Walter, V. Kumar, A. Krust, J. M. Bornert, P. Argos and P. Chambon 1986 Human oestrogen receptor cDNA: sequence, expression and homology to v-erb-A. Nature 320: 134-139.

Guntaka, R. W., A. S. Rao, T. T. Green, and W. E. Collins 1986 Specific detection of *Plasmodium falciparum* malaria by a molecularly cloned DNA probe. Biochem. Biophys. Res. Commun. 138: 363-368.

Gusella, J. R., R. E. Tanzi, P. I. Bader, M. C. Phelan, R. Stevenson, M. R. Hayden, K. J. Hoffman, A. G. Faryniarz, and K. Gibbons 1985 Deletions of Huntington's disease-linked G8 (D4S10) locus in Wolf-Hirschorn syndrome. Nature 318: 75-78.

Kan, Y. W. 1986 The William Allan Memorial Award Address: Thalassemia: Molecular mechanism and detection. Am. J. Hum. Genet. 38: 4-12.

Koch, T. K., B. O. Berg, S. J. DeArmond, and R. F. Gravina 1985 Creutzfeldt-Jakob disease in a young adult with idiopathic hypopituitarism. Possible relation to the administration of cadaveric human growth hormone. New Eng. J. Med. 313: 731-738.

Lewin, R. 1986a Molecular biology of *Homo sapiens*. Science 233: 157-160.

——— 1986b Proposal to sequence the human genome stirs debate. Science 232: 1598-1560.

Marx, J. 1985 Plant gene transfer becomes a fertile field. Science 230: 1148-1150.

McKusick, V. A. 1986a Molecular biology of *Homo sapiens*. Cold Spring Harbor Symposium on Quantitative Biology, Vol LI. In press.

——— 1986b The morbid anatomy of the human genome: A review of gene mapping in clinical medicine. Medicine 65: 1-33.

Milner, P. D. A. 1986 Which children should have growth hormone therapy? Lancet 1: 483-485.

Monaco, A. P., C. J. Bertelson, W. Middlesworth, C. A. Colletti, J. Aldridge, K. H. Fishbeck, R. Bartlett, M. A. Pesicak-Vance, A. D. Roses, and L. M. Kunkel 1985 Detection of deletions spanning the Duchenne muscular dystrophy locus using a tightly linked DNA segment. Nature 316: 842-845.

Nathans, J., D. Thomas and D. S. Hogness 1986 Molecular genetics of human color vision: The genes encoding blue, green and red pigments. Science 232: 193-202.

Newmark, P. 1986 DNA fingerprints go commercial. Nature 321: 104.

Otten, A. L. 1985 Wrongful life? Parents and newborns win new legal rights to sue for malpractice. Failing to do prenatal tests and to advise abortions opens physicians to suits. Wall St. J. LXV, No. 165, 1.

Rigl, C. T. 1986 Scale up technology and talent deficiencies threaten U.S. lead in biotech. Genetic Eng. News 6: 40.

Schmidtke, J., M. Krawczak, and D. N. Cooper 1986 Human gene cloning: the storm before the lull? Nature 322: 119.

Sudhof, T. C., M. S. Brown, J. L. Goldstein, and D. W. Russell 1985 The LDL receptor: a mosaic of genes shared with different proteins. Science 228: 815-824.

Taylor, W. N. 1986 Synthetic hGH should be classified as a controlled substance to prevent abuse. Genetic Eng. News 6: 4-37.

White, R. L. 1985 Diagnosis when the gene locus is unknown. Hosp. Prac. 20(5): 103-113.

Williamson, R. 1985 Cloned genes and their use in the analysis of inherited disease. Biochem. Soc. Trans. 13: 807-811.

Willis, A. E. and T. Lindahl 1987 DNA Ligase I deficiency in Bloom's syndrome. Nature 325, 355-357.

Wion, K. L., E. S. D. Tudderham and R. M. Lawn 1986 A new polymorphism in the factor VIII gene for prenatal diagnosis of hemophilia A. Nucl. Acids Res. 14: 4535-4542.

Yanofsky, R. A., A. Beadry, D. J. Ferguson, K. Pearse, E. M. Rubin and Y. W. Kan 1986 Survival of a hydropic infant with α thalassemia. Blood 64(Suppl) 60a.